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Claims 1-8, 10-15 and 17-25 are currently pending after the above claim amendments. Claims 1, 2, 8, 10, 15, 17 and 23 have been amended to more particularly point out and distinctly claim that which the applicant considers to be the invention. The claim amendments are offered in part to make clear that the claimed treatments of patients are understood to be through the direct administration of the RID complex to the target cells.

Applicant notes with appreciation the withdrawal of the rejection of claims 1-25 as being vague and indefinite, and the rejection of claim 23 as being vague and indefinite. Additionally, applicant appreciates the finding in the Office Action at page 2 that the specification enables a method for inhibiting/decreasing apoptosis comprising direct administration of the RID α and RID β polypeptide to target cells in a liposome composition to facilitate entry into the cells.

Applicant also notes with appreciation the allowability of claims 4, 7, 13-14, 17-22 and 25 if rewritten in independent form, including all of the limitations of the base claim and any intervening claims. However, it is noted that claim 17 is an independent claim and that claims 18-22 are all ultimately dependent only on claim 17. Therefore, applicant respectfully requests the allowance of claims 17-22.

Rejections under 35 U.S.C. 112

Applicants notes with appreciation the withdrawal of the rejection of claims 1-3, 5-12, 14-19, and 21-24 under 35 U.S.C. 112, first paragraph (at page 2 of the Office Action), along with the holding that the arguments and declaration of April 12, 2000 were persuasive with regard to the enablement of the specification with effective dosage and stability issues (at page 12-13 of the Office Action). However, the following new rejections under 35 U.S.C. 112, first paragraph were entered.

Claims 1, 8-10, 14-17 and 21-23 stand rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for "any and all routes of administration of a RID peptide complex for the treatment of any and all diseases/disorders treated by inhibiting or decreasing apoptosis in any and all patient." Enablement is also asserted to be lacking because "... the specification does not provide a correlation between RID delivery to the alleviating degenerative disease or an immunodeficiency disease" (page 4 of the Office Action) and that particulars of route of administration, dosages, and treatment protocols (page 5). Applicant respectfully requests reconsideration and withdrawal of the rejection in light of the claim amendments and the following remarks.

[Applicant first points out that claims 1, 8, 9 and 21 are not directed to the treatment of a patient.] Therefore, none of the asserted disease treatment enablement deficiencies would apply to these

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claims. In this regard, Applicant points out that the claims directed to treatment of cells of a patient (claims 10, 14-17, 21 and 22) do not require the alleviation of disease symptoms or the reduction in disease. They only require a decrease in apoptosis in the treated cells. Although the claims do not require that such a treatment can cure or alleviate symptoms of any disease, the claimed reduction in apoptosis could nonetheless be useful for treating the disease, e.g., in combination with other treatments, etc. Applicant also notes that the amended claims are all limited to direct administration of cells with the RID complex, which is abundantly enabled in the specification, e.g., in the examples (see following discussion of examples). Indeed, the PTO agrees that the specification is enabling for inhibiting/decreasing apoptosis by direct administration of a RID complex to a cell in a liposome (see page 2 of July 14, 2000 Office Action) and that the specification is enabled for inhibiting apoptosis *in vitro* by direct contact of a cell line with an expression vector comprising a nucleic acid encoding RID complex in operable linkage with a promoter (page 8 of Office Action). With regard to the asserted lack of enablement for particular routes of administration, dosages and treatment protocols, applicants first note that the present Office Action, at pp. 12-13, that such parameters were found to be enabled based on the arguments and declaration filed April 12, 2000. Applicants also point out that the claims now clearly require that the RID complex be administered directly to the cells, and contend that determining those aspects of the invention could be determined for any particular cell treatment, particularly since the specification provides several examples which give dosages and provides protocols for administration to cells. See, e.g., in Example 2, where plasmids expressing RID component polypeptides are used to transfect mammalian cells, and the effect of the presence and absence of the RID complex upon apoptosis of the cells is demonstrated; in Example 3, where an adenovirus vector was used to transfect human cells to demonstrate clearing of Fas; in Example 4, where human A549 cells were infected with viral vectors that were positive or negative for the expression of RID complex polypeptides, and clearing of Fas from the cell surface was measured; in Example 5, where human MCF7 cells were infected with wild-type or mutant adenovirus to demonstrate that signal receptors are degraded in lysosomes; in Example 6, where COS cells were transiently transfected with plasmids containing various RID complex components and it was shown that Fas was cleared from the surface of the cells by the complete RID complex; in Example 7, where lymphocytes withdrawn from mice infected with influenza virus were activated and incubated with RID⁺ and RID⁻ mouse cells to show that RID inhibited CTL cell killing through the Fas pathway; and in Example 8, where human HeLa cells infected with viral RID polynucleotides and with the 231-10 vector RID polynucleotides showed the internalization and destruction of Fas and TNFR1.

See also Wold declaration of April 12, 2000 at page 4-5. Based on the above discussion, the rejected claims are clearly enabled as amended. Applicant therefore respectfully requests reconsideration and withdrawal of the rejection of claims 1, 8-10, 14-17 and 21-23 under 35 U.S.C. 112, first paragraph.

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Claims 1-7, 10-14, 17-20 and 24-25 stand rejected under 35 U.S.C. 112, first paragraph as lacking enablement for any and all routes of administration, and treating any and all patients suffering from any and all diseases/disorders such as degenerative disease or immunodeficiency disease. Applicants respectfully request reconsideration and withdrawal of this rejection in light of the claim amendments, the discussion of the rejection of claims 1, 8-10, 14-17 and 21-23 above, and the following remarks.

The apparent primary objection to these claims are that targeting gene therapy treatments to specific cell types or locations is asserted to be an unpredictable art. Applicants first point out that the [current claims are now limited to the direct treatment of cells.] It is believed that this would render the objection to the targeting aspects of the current claims moot, since the targeted cells are directly treated. Further, at the middle of page 8, the current Office Action states that the claims are enabled for inhibiting apoptosis *in vitro* where the claim is specifically directed to contacting a cell line with an expression vector comprising a nucleic acid encoding RID complex in operable linkage with a promoter. [It is also noted that claims 1-8 and 24-25 are not directed to treatment of patients. Thus, those claims should not be affected by any aspect of this rejection that relates to treatment of disease.] See the discussion of the rejection of claims 1, 8-10, 14-17 and 21-23 above for further elaboration of this point. For the above reasons, applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1-7, 10-14, 17-20 and 24-25 under 35 U.S.C. 112, first paragraph.

Claims 4, 13, 20, and 25 stand rejected under 35 U.S.C. 112, first paragraph as failing to provide an enabling disclosure. It is asserted that the 231-10 vector is not obtainable by any repeatable method set forth in the specification, or is otherwise not available to the public. Applicant again maintains that the 231-10 vector can be made by the skilled artisan, not only by the methods disclosed in the specification, but also by any of a number of methods that would be readily apparent to the skilled artisan, given that the specification discloses the nucleotide sequence of the plasmid in Figure 27, as well as SEQ ID NO:5. The skilled artisan would know that the method disclosed in Example 10 is not the only way to produce the plasmid with the sequence of SEQ ID NO:5. For example, the skilled artisan could, without undue experimentation, simply obtain an adenovirus serotype 5, which is available from the American Type Culture Collection (ATCC), make the proper deletions from that virus by well established methods, create an E3 transcription unit identical to the *pm734.1* E3 unit by cloning them from the adenovirus 5 and adenovirus 3 (also available from ATCC) E3 units, recombine them in the proper sequence, and create the proper missense mutations in the *adp* gene, all methods that are well within the ability of any skilled molecular biologist without undue experimentation. Then, the skilled artisan could easily clone the CMV promoter from a cytomegalovirus, also available from ATCC, and clone that in the proper place, which is

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easily performed without undue experimentation, to create the 231-10 vector. All of the above methods could be performed using materials available from ATCC without undue experimentation. The skilled artisan would also know that there are many other ways that the sequence given in SEQ ID NO:5 could be created using well known methods such as those described above. In light of these remarks, applicant respectfully requests reconsideration and withdrawal of the rejection of claims 4, 13, 20, and 25 under 35 U.S.C. 112, first paragraph.

Claims 1-22 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite. It is asserted that the step "an effective amount of a Receptor Internalization and Degradation complex" does not correlate with the inhibition of apoptosis. Applicant notes that claims 1, 10 and 17 (to which the other rejected claims depend) have been amended to more definitely make the correlation between "effective amount" and inhibiting apoptosis. In light of these claim amendments, applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1-22 under 35 U.S.C. 112, second paragraph.

Rejections under 35 U.S.C. 102

Claims 1-3, 5, 10-13 and 24 stand rejected under 35 U.S.C. 102(b) as being anticipated by Dimitrov et al. (August 1997), *J. Virol.* 71:2830-2837. Applicant respectfully requests reconsideration and withdrawal of this rejection because the reference was published after the priority date of July 7, 1997 (U.S. Provisional Application No. 60/088,993) and is therefore unavailable as prior art. Applicant also states in the enclosed declaration under 37 C.F.R. 1.132 that the work in that publication is the author's own work.

Claims 1-3, 5-6, 8-12, 15-16 and 24 stand rejected under 35 U.S.C. 102(a) as being anticipated by Krajcsi et al. (August 1996), *J. Virol.* 70:4904-4913. In response to this rejection, applicant has submitted a declaration under 37 C.F.R. 1.132 stating that the cited reference represents applicant's own work and therefore should not be considered as prior art.

Claims 1-3, 5, 8-12, 15-16 and 24 stand rejected under 35 U.S.C. 102(b) as being anticipated by Stewart et al., 1995, *J. Virol.* 69:5871-5881. Applicant respectfully requests reconsideration and withdrawal of this rejection based on the following discussion. The PTO states that Stewart et al. teaches that the RID complex is localized to the plasma membrane, that both proteins are required for plasma membrane localization, that certain adenovirus mutants confer preventive or protective functions, and that the RID complex interferes with the function of membrane-associated proteins that participate in TNF signaling. However, the PTO correctly does not state that Stewart et al. treats a cell with a RID complex to inhibit apoptosis; nor does Stewart et al. suggest that such a treatment would be successful. Since Stewart et al. does not disclose the claimed method, applicant asserts that it does not anticipate the claims.

2. I am one of the co-authors of the publication, Dimitrov et al., 1997, Adenovirus E3-10.4K/14.5K Protein Complex Inhibits Tumor Necrosis Factor-Induced Translocation of Cytosolic Phospholipase A2 to Membranes, *J. Virol.* 71:2830-2837. All of that work was done under my direction, and all aspects of the present invention reflected in that publication were conceived by me.

3. I am also one of the co-authors of the publication, Krajcsi et al., 1996, The Adenovirus E3-14.7K Protein and the E3-10.4K/14.5K Complex of Proteins, Which Independently Inhibit Tumor Necrosis Factor (TNF)-Induced Apoptosis, Also Independently Inhibit TNF-Induced Release of Arachidonic Acid, *J. Virol.* 70:4904-4913. All of that work was done under my direction, and all aspects of the present invention reflected in that publication were conceived by me.

4. I further declare that all statements herein made by my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardized the validity of the above-identified application.

Dated: _____

William S. M. Wold, Ph.D.